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Acceleration of Lung Maturation in a Human Fetus following Maternal Isotretinoin Intake

Jean-Claude Fauchère^a Jörg Ersch^{a, c} Daniel Allen Grant^d
Roland Zimmermann^b Hans Ulrich Bucher^a Thomas Stallmach^c

^aClinic of Neonatology, ^bClinic of Obstetrics, ^cPediatric and Developmental Pathology, Department of Pathology, University Hospital Zurich, Zurich, Switzerland; and ^dRitchie Centre for Baby Health Research, Fetal and Neonatal Physiology, Monash Institute of Medical Research, Monash University, Clayton, Australia

Key Words

Isotretinoin • Retinoids • Lung maturation • Prematurity • Glucocorticosteroids

Abstract

The viability of the human fetus increases significantly beyond 25 weeks' gestation as the lung development progresses towards the 'saccular' stage. We report on a fetus of 22 weeks' gestation whose lung maturation was accelerated by 4 weeks, most likely due to the unintentional exposure to the retinoid isotretinoin (13-*cis*-retinoic acid) during pregnancy. Although retinoids are known to be stored within the lungs and to play a key role in lung differentiation and growth, their storage within the lung is limited during this critical developmental period. Even though glucocorticosteroids are used clinically to enhance lung maturation in the face of impending preterm birth, there are no data yet which demonstrate that glucocorticosteroids, when given alone, are effective in promoting lung maturation prior to 24 weeks' gestation. Strong evidence however, indicates that glucocorticosteroids promote the utilization of lung retinoids immediately before birth. Our observation of increased lung maturation, in conjunction with the above information suggests that retinoids alone or in combination with glucocor-

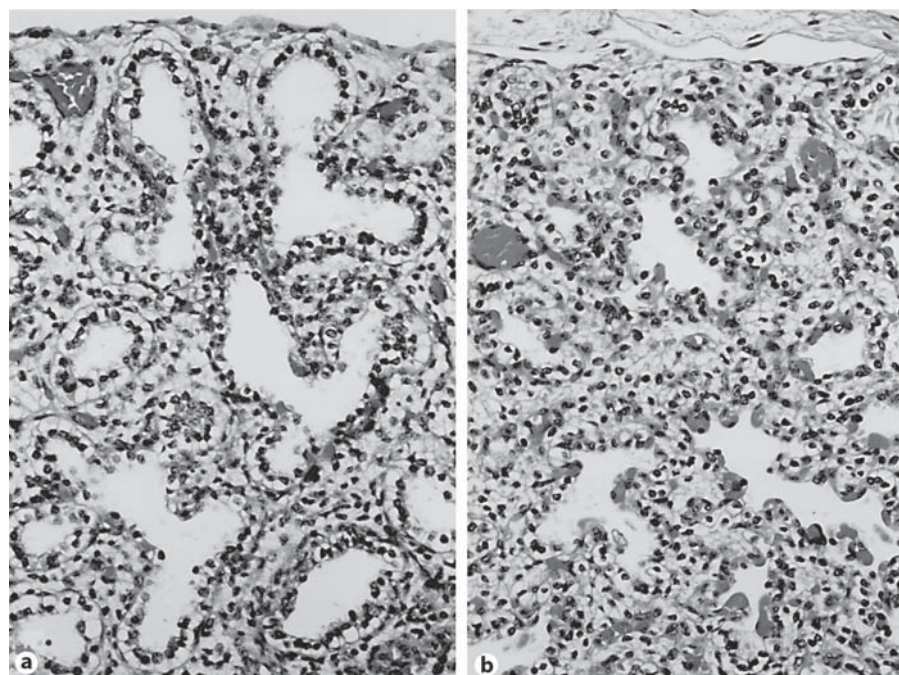
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Introduction

Survival after premature birth is largely dependent upon the maturational stage of the lung. At approximately 25 weeks' gestation, the lungs undergo an anatomical transition from the 'canalicular' to the 'saccular' stage [1]. This is heralded by the differentiation of the cuboidal epithelial lining of the future airway spaces, and also by the enlargement of the pulmonary capillary bed which begins to form extended contact with the future air spaces. From animal studies, it has long been known that retinoids have a profoundly stimulating effect on lung growth and maturation [2]. This beneficial effect of retinoic acid (RA) is mainly true for the initial outgrowth, and for later alveogenesis, while in between, RA have been shown to rather inhibit branching morphogenesis. They have a true maturational effect on the lung epithelium. They also accelerate fetal lung branching, leading to the development of the alveolar tree [3], and favor choline incor-

Fig. 1. Advanced maturation of the bronchoalveolar tree (lower lung lobe). **a** The typical canalicular stage of lung development in a normal fetus at 22 weeks' gestational age shows airways lined by a cuboidal epithelium with a few capillaries reaching the lumen. **b** The lungs of a fetus with high maternal intake of isotretinoin reveals a saccular stage where capillaries have already formed frequent contacts to the lumen of many alveolar spaces, more in keeping with a gestational age of 26 weeks. HE. $\times 250$.



poration into phosphatidylcholine [4]. At present, the only widely accepted method to stimulate pulmonary maturation before preterm birth is through antenatal administration of glucocorticosteroids to the mother. However, for this to be effective, birth must be postponed for at least 24–48 h, and there must be a sufficient number of type II pneumocytes as the main action of glucocorticosteroids is to increase surfactant production, and not to promote further structural development. Another, less well known mechanism of action of steroids is to increase the utilization of lung retinyl palmitate stores and promote the consumption of retinol. Geervarghese and Chytil have shown that the depletion of pulmonary vitamin A stores before birth, which is necessary for lung differentiation, is enhanced by administering dexamethasone [5].

Case Report

A 23-year-old woman began treatment with isotretinoin (Roaccutan®, 30 mg daily) for severe acne. Two months later, she unknowingly became pregnant and it was not until 20 weeks' gestation that she consulted a physician. The probability of fetal malformations was considered sufficient to recommend termination of pregnancy. An abortion was therefore induced at 22 weeks. The intake of isotretinoin was never discontinued.

The male fetus did not show any gross anomalies or malformations; body size measurements and organ weights were all within the normal range for gestational age. No signs of hydrocephalus and no external ear malformations were found. Special attention was paid to the brain which showed a gyration pattern and a neuronal stratification corresponding to 22 weeks' gestational age. Similarly, skin development also indicated that the fetus was not older than 22 weeks' gestation [6]. The only finding discordant to the gestational age of 22 weeks was a striking development acceleration in lung morphology. Normally in the human fetus at 22 weeks, the future airways are lined with a cuboidal epithelium, and a capillary network is found on the stromal side of the epithelial cells. In this so-called 'canalicular' stage, capillaries regularly extend between the epithelial cells and occasionally touch the luminal space (fig. 1a). This fetus presented a pulmonary morphology of both lower lung lobes which differed in several aspects from what is normally seen at 22 weeks. Cuboidal epithelial lining was only observed in a limited amount of subpleural lung tissue. Moreover, the capillary bed was well advanced as capillaries formed frequent and broad contact to the luminal space (fig. 1b). In summary, postmortem results demonstrated that the lungs of this fetus had reached a morphological stage of maturation (saccular stage) that is usually seen at approximately 26 weeks' gestation, while all other postmortem indications were in keeping with a gestational age of 22 weeks.

Discussion

To our knowledge, this is the first report of a human fetus whose lung maturation may have been significantly accelerated by unintentional exposure to isotretinoin. Our observation extends to the human the numerous earlier observations from in vitro and animal research that vitamin A compounds (retinoids) play a key role in lung differentiation, growth and healing [3, 4, 7–10]. In the situation of some uncertainty regarding gestational age, we took great care not only to rely on body size measurements and organ weights to assess gestational age as precisely as possible. We also used several accepted more reliable methods such as foot length, brain development and skin histology [6]. Although a gestational age of 22 weeks was estimated by these methods, the lung histology of this fetus, assessed by 2 independent highly trained examiners, was in keeping with that of a more mature 26 weeks' gestation fetus. As the mammalian lung maturation progresses from apical to basal, we routinely examine both lower lung lobes (central and peripheral areas) when trying to determine lung maturation.

Fetal lung development is accelerated by retinoids in both in vivo animal studies [4] and in studies of cultured lung tissue [11]. Retinoids are known to accelerate fetal lung branching leading to the development of the alveolar tree and also promote the expression of some genes coding for surfactant proteins and enzymes in the production of their lipid component [3]. It is not completely clear whether this acceleration effect is caused by a direct effect on epithelial differentiation, by interactions with mesenchymal cells [12], or in concert with mediators, i.e. interleukins [3].

A major concern in recent years has centered around the teratogenic effects of very high doses of 13-*cis*-isotretinoin. A study on teratogenicity of high vitamin A intake (> 10,000 IU/day) in over 22,000 pregnant women did not observe any birth defects when vitamin A supplementation was started after week 7 [13]. Korte et al. [14] found RA embryopathies in monkeys only when the exposition to 13-*cis*-RA occurred in the period preceding organogenesis. For the human being, this teratogenically sensitive period occurs over 3–8 weeks after conception (corresponding approximately to gestational weeks 5–10) [15]. As stated by Chytil, the teratogenic effects of high doses of retinoids during embryogenesis have overshadowed the key role that retinoids play in normal cellular differentiation during fetal life [3].

Not only have retinoids been shown to be importantly involved in the induction and regulation of alveogenesis,

there is also increasing support for their possible therapeutic value in humans [9]. Bronchopulmonary dysplasia, one of the major long-term burdens of prematurity, presents in a classical form with inflammation, fibrosis and smooth muscle hypertrophy. More recently, bronchopulmonary dysplasia has also presented in a new form in extremely preterm infants born just when alveolarization of the distal lung saccules is beginning, which arrests alveolar and vascular development [16, 17]. Both forms of bronchopulmonary dysplasia result in a lung deficient in alveoli, and therefore deficient in gas exchange area. Vitamin A and its analogues have been proposed for the prevention and treatment of bronchopulmonary dysplasia, and clinical trials have been conducted in prematurely delivered infants [18]. As the storage of vitamin A and its compounds in the lungs occurs during the latter third of pregnancy [19], premature infants <37 weeks' gestation have limited vitamin A stores [20, 21]. Several authors have also shown that pulmonary vitamin A stores deplete shortly before birth [4, 22], indicating an increased demand for retinoids in the crucial periods of lung differentiation. Moreover, postnatal glucocorticosteroids may impact on lung development by inhibiting alveolarization [10, 23], and RA, a biologically active derivative of vitamin A, has been shown in the animal model to block this inhibitory effect or to restore gas exchange area [10, 24]. Whether histological regeneration of the alveoli also translates into a functional recovery still remains to be elucidated [25].

Glucocorticosteroids are administered to a pregnant mother when in danger of delivering prematurely, and they increase surfactant production. Unfortunately glucocorticosteroids only prevent respiratory distress syndrome in approximately 40–50% of cases [26], and repetitive courses seem not to be of further benefit [27]. Another mechanism by which glucocorticosteroids promote lung maturation is an increased utilization of lung retinyl palmitate stores and the consumption of retinol, as shown by Geevarghese and Chytil [5] using dexamethasone. Similarly, steroids given antenatally to rhesus monkeys [28] and pregnant women [29] increased both maternal and fetal concentrations of retinol-binding protein, pointing to the critical link between steroidal efficacy and retinoid utilization.

Our report of the documented intake of 30 mg/day of isotretinoin up to the day of delivery in a nonviable fetus of 22 weeks' gestational age demonstrates that maturation of the lungs in a human fetus may be strongly accelerated by retinoids at that early stage of gestation. This fetus demonstrated a spatial relationship of epithelium

and capillaries corresponding to a fetus of 26 weeks. There is no evidence that glucocorticosteroids are effective in promoting lung maturation before 24 weeks. However, given the links between glucocorticosteroids and retinoid compounds, a combined therapy of these agents might propel lung maturation more effectively than each compound in isolation when the clinician is faced with an impending premature birth at the limits of viability. The possible advantages of retinoids in lung differentiation when applied in the days before preterm delivery when stores are low, and the potentially additive effects

of glucocorticosteroids have not yet been extensively explored.

Although the information of our case report does not allow more firm conclusions, our observation provides the enticing prospect that RA, or its derivatives may one day serve as a valuable preventive or therapeutic tool in cases of extreme prematurity. Before our observation can be translated into safe clinical reality for tiny preterm infants, extensive research and development will be required to answer the many questions related to formulation, efficacy and safety.

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